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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,452	ANKER ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *7-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending.

1. Applicant's election without traverse of Group I, claims 1-6 and 19-22 and liver cirrhosis as a specific disease and ursodesoxycholic acid (UDCA) as specific bile acid in Response to Restriction Requirement, filed on 04/13/04 is acknowledged.

Claims 7-18 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-6 and 19-22, drawn to a method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, comprising administering to a patient an effective amount of a compound that is able to reduce the production, adsorption or effect of endotoxin, wherein the compound is a bile acid are under consideration in the instant application.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

3. Claim 19 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim 19 should refers to other claims in the alternatives only. See MPEP § 608.01(n).

4. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in United Kingdom on 03/09/1999 . It is noted, however, that applicant has not filed a certified copy of the 9905315.9; 9905300.1;9905310.0;9905307.6;9905314.2 applications as required by 35 U.S.C. 119(b).

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6 and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1-3 are indefinite and ambiguous in the recitation of endotoxin (lipopolysaccaride; LPS). It is unclear if the term LPS that is placed in parenthesis refers to endotoxin or to lipopolysaccaride.

8. Claim 2 is indefinite and ambiguous in the recitation of "preventing or ameliorating endotoxin-mediated immune activation..." . There is insufficient antecedent basis for this limitation in the claim, since base Claim 1 does not recite "preventing".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the LPS-stimulated cytokine production in patients with cachexia, comprising administration of UDCA, does not reasonably provide enablement for a method of treating or ameliorating body wasting or cachexia in a patient with various diseases as recited in claim 1, for example liver cirrhosis, comprising administering to a patient an effective amount of a compound that is able to reduce the production, adsorption or effect of endotoxin, wherein the compound is *a* bile acid as recited in claim 6, for example UDCA; or for a method of preventing endotoxin-mediated body wasting or cachexia in a patient with various diseases as recited in claim 2, for example liver cirrhosis, comprising administering to a patient an effective amount of a compound that is able to reduce the production, adsorption or effect of endotoxin, wherein the compound is *a* bile acid as recited in claim 6, for example UDCA; The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.
The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses detailed *in vitro and in vivo* studies that administration of UDCA can inhibit the LPS-stimulated cytokine production of whole blood of patients with cachexia. The specification does not adequately teach how to effectively treat or ameliorate body wasting or cachexia in a patient with various diseases as recited in claim 1, for example liver cirrhosis, by administering to said patient an effective amount of *a* bile acid as recited in claim 6 , for example UDCA. Moreover, no animals models were used to study the effectively of treating or ameliorating body wasting or cachexia in a patient with various diseases as recited in claim 1, for example liver cirrhosis, comprising administering an effective amount of *a* bile acid, for example UDCA. Since there is no animal model studies and data in the specification to show the effectively of treating or ameliorating body wasting or cachexia in a patient with various diseases as recited in claim 1, for example liver cirrhosis, comprising administering an effective amount of a bile acid, for example UDCA, it is unpredictable how to correlate limited *in vitro* results with *in vivo* use. The specification does not provide sufficient teaching as to how it can be assessed that treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis was achieved after the administration of a therapeutically effective amount of a bile acid, for example UDCA. Trauner et al., (IDS) teach that UDCA is of unproven efficacy in non-cholestatic disorders, including liver diseases (see entire document, Abstract in particular). Moreover, Applicant acknowledges that the effects of UDCA are conflicting (see page 5 of the Specification as filed). In addition, Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". In addition, Cochlovius et al (Modern Drug Discovery, 2003, pages 33-38) teach that in contrast to in vitro models, and partly animal-human xenograft systems, tissue cells in vivo seems to express molecules for defense against cellular immune systems as well as against complement. Although these defense mechanisms are still poorly understood, they provide some hints as to why many potential therapeutics perform marvelously in vitro but a fairly high portion of them still fail in vivo. Moreover, an effective protocol for a method of treating or ameliorating body wasting or cachexia in a patient with various diseases as recited in claim 1, for example liver cirrhosis, is subject to a number of factors which enter the picture beyond simply the administration to the subject an effective amount of any bile acid, for example UDCA. Demonstrating *in vitro and in vivo* that administration of UDCA can inhibit the LPS-stimulated cytokine production of whole blood of patients with cachexia cannot alone support the predictability of a method of treating or ameliorating body wasting or cachexia in a patient with various diseases as recited in claim 1, for example with liver cirrhosis by administration to the subject an effective amount of bile acid,

for example UDCA. Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect immune response such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to enhance an immune response will vary depending upon factors such as the condition of the host and burden of disease.

Also the issue that, the burden of enabling the prevention of endotoxin-mediated body wasting or cachexia in a patient with various diseases as recited in claim 2, for example liver cirrhosis (i. e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to endotoxin-mediated body wasting or cachexia in a patient with various diseases as recited in claim 2, for example liver cirrhosis, within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing these disease states. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of treating or ameliorating body wasting or cachexia in a patient with various diseases as recited in claim 1, for example liver cirrhosis, comprising administering to a patient an effective amount of a compound that is able to reduce the production, adsorption or effect of endotoxin, wherein the compound is *a* bile acid as recited in claim 6, for example UDCA; or for a method of preventing endotoxin-mediated body wasting or cachexia in a patient with various diseases as recited in claim 2, for example liver cirrhosis, comprising administering to a patient an effective amount of a compound that is able to reduce the production, adsorption or effect of endotoxin, wherein the compound is *a* bile acid as recited in claim 6, for example UDCAA in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.

8. Claim 1-6 and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5639744 as evidenced by US Patent 4377595 and/or US Patent 4,898,879.

US Patent '744 teaches a method of treating liver diseases, including liver cirrhosis, comprising administering to a patient an effective amount of UDCA (see entire document, Abstract and column 3 in particular). US Patent '884 teaches various ways of administering UDCA, including orally administration (see column 3 in particular).

As is evidenced by US Patent 4377595 (see entire document, column 3 in particular) and/or US Patent 4,898,879 (see entire document, column 4 in particular) the diseases such as cirrhosis of the liver results in a body wasting or cachexia and restoring liver function would be beneficial for the patient with weight loss. Thus a method of treating liver diseases, including liver cirrhosis, comprising administering to a patient an effective amount of UDCA as taught by US Patent ' 744 would inherently results in treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis. Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02.

The references teaching anticipates the claimed invention.

9. Claim 1-6 and 19-21 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,251,884 as evidenced by US Patent 4377595 and/or US Patent 4,898,879.

US Patent '884 teaches a method of treating liver diseases, including liver cirrhosis, comprising administering to a patient an effective amount of UDCA (see entire document, Abstract and column 2 in particular). US Patent '884 teaches various ways of administering UDCA, including orally and intravenously administration (see column 4 ,8 and 13 in particular).

As is evidenced by US Patent 4377595 (see entire document, column 3 in particular) and/or US Patent 4,898,879 (see entire document, column 4 in particular) the diseases such as cirrhosis of the liver results in a body wasting or cachexia and restoring liver function would be beneficial

for the patient with weight loss. Thus a method of treating liver diseases, including liver cirrhosis, comprising administering to a patient an effective amount of UDCA as taught by US Patent 6,251,884 would inherently results in treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis. Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02.

The reference teaching anticipates the claimed invention.

10. Claim 1-6 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,869,265 as evidenced by US Patent 4377595 and/or US Patent 4,898,879.

US Patent '265 teaches a method of treating liver diseases, including liver cirrhosis, comprising administering to a patient an effective amount of UDCA (see entire document, Abstract and column 35, Example IX in particular).

As is evidenced by US Patent 4377595 (see entire document, column 3 in particular) and/or US Patent 4,898,879 (see entire document, column 4 in particular) the diseases such as cirrhosis of the liver results in a body wasting or cachexia and restoring liver function would be beneficial for the patient with weight loss. Thus a method of treating liver diseases, including liver cirrhosis, comprising administering to a patient an effective amount of UDCA as taught by US Patent ' 265 would inherently results in treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis. Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02.

The references teaching anticipates the claimed invention.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-6 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,251,884 or US Patent 5,869,265 or US Patent 5639744 each in view of US Patent 4377595 and/or US Patent 4,898,879.

The teaching of US Patent ' 884 or US Patent ' 265 or US Patent ' 744 have been discussed, supra.

The claimed invention differs from the reference teaching in that the US Patent ' 884 or US Patent ' 265 or US Patent ' 744 does not teach a method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, comprising administrating an effective amount of UDCA .

US Patent'595 teaches that the diseases such as cirrhosis of the liver results in a body wasting or cachexia (see column 3 in particular).

US Patent '879` teaches that liver diseases such as cirrhosis of the liver results in a significant body wasting or cachexia and that restoring liver function would be beneficial for the patient with weight loss (see column 4 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent'595 or US Patent '879 to those of US Patent ' 884 or US Patent ' 265 or US Patent ' 744 to obtain a claimed method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, comprising administrating an effective amount of UDCA .

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because there is a direct correlation between liver diseases such as cirrhosis of the liver and body wasting or cachexia and treating cirrhosis of the liver would be beneficial for the patient with weight loss as taught by US Patent'595 and US Patent '879. Treating cirrhosis of the liver can be done by administering to a patient an effective amount of UDCA are taught by US Patent ' 884 or US Patent ' 265 or US Patent ' 744 . The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some

advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Claims 2-4 are included because the claimed functional limitation would be an obvious properties of the referenced method of treating liver cirrhosis comprising administering of UDCA. It is clear that both the prior art and claimed method administer the same compound, i.e. UDCA to the same patient, i.e. a patient with liver cirrhosis to achieve the same results. Since the reference method administering the same compound as claimed , it would be obvious that UDCA would be able to reduce the production, absorption and/or the effect of an endotoxin or reduce the available endotoxin in the patient as claimed. When the prior art method is the same as a method described in the specification, it can be assumed the method will obviously perform the claimed process absent a showing of unobvious property.

Claim 22 is included because it would be conventional and within the skill of the art to determine the optimum routes of UCDA administration . Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum routes of administration involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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